CLAIMS

1. A method of enriching for and identifying a nucleic acid sequence difference with respect to a reference sequence comprising:

a) contacting a nucleic acid sample with a molecule comprising a sequence-specific binding activity under conditions which permit specific binding, wherein said sample comprises a subset of nucleic acid molecules having a sequence that binds to said sequence-specific binding activity, and wherein a bound subset of nucleic acid molecules is retained by the sequence-specific binding activity, such that the subset of bound nucleic acid molecules is enriched for molecules comprising the sequence recognized by the sequence specific binding activity; and

b) detecting a sequence difference with respect to a reference sequence in the subset of nucleic acid molecules.

2. The method of claim 1 wherein the molecule comprising sequence-specific binding activity is selected from the group consisting of: transcription factors or DNA binding domains thereof; proteins with zinc-finger DNA binding domains; restriction endonuclease DNA recognition domains; sequence-specific antibodies; oligonucleotides complementary to an adapter ligated to a population of DNA molecules; nucleic acid molecules; aptamers; peptide nucleic acid molecules; peptides; and affinity resins which recognize DNA having a particular G+C content or methylation status.

3. The method of either of claims 1 or 2 wherein said sequence-specific binding activity is bound to a solid support.

4. A method of identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) cleaving a nucleic acid sample from one or more individuals with one or more sequence-specific cleavage agents to produce nucleic acid fragments;

b) operatively linking said fragments with molecules capable of being replicated;

c) introducing the linked molecules of step (b) into a system capable of replicating only a subset of said linked molecules, and replicating said subset to form a collection of replicated molecules; and

d) detecting one or more nucleic acid sequence differences with respect to a reference sequence in the members of said collection of step (c) with a method capable of detecting one or more nucleotide differences with respect to a reference sequence.

5. The method of claim 4 wherein said system capable of replicating said linked molecules comprises host cells and the collection of replicated molecules comprises a library.

6. The method of claim 4 wherein said method capable of detecting one or more nucleotide differences comprises DNA sequencing.

7. The method of claim 4 wherein said method capable of detecting one or more nucleotide differences comprises denaturing HPLC.

8. The method of claim 4 wherein said method capable of detecting one or more nucleotide differences comprises electrophoresis capable of detecting conformational differences in the nucleic acids.

9. The method of claim 4 wherein said method capable of detecting one or more nucleotide differences comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid.

10. The method of claim 6 wherein said sequencing is performed using primers that hybridize to the molecules capable of being replicated.

11. The method of claim 4 wherein said system capable of replicating said linked molecules comprises in vitro replication of said linked molecules.

12. The method of claim11 wherein said in vitro replication comprises a step utilizing primers for nucleic acid polymerization that hybridize specifically to said molecules capable of being replicated.

13. The method of claim 11 wherein said in vitro replication comprises a step utilizing primers for nucleic acid polymerization that hybridize specifically to sequences comprising both a segment of said molecules capable of being replicated and the fragment ends of a subset of the nucleic acid molecules linked to said molecules capable of being replicated.

14. The method of claim 4 wherein said cleavage agents are restriction endonucleases.

15. The method of claim 14 wherein at least one restriction endonuclease cleaves DNA infrequently.

16. The method of claim 15 wherein the infrequently cleaving restriction endonuclease is selected from the group consisting of AscI, BssHII, EagI, NheI, NotI, PacI, PmeI, RsrII, SalI, SbfI, SfiI, SgrAI, SpeI, SrfI, and SwaI restriction endonucleases.

17. A method of identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) cleaving a nucleic acid sample from one or more individuals with one or more sequence-specific cleavage agents to produce nucleic acid fragments;

b) operatively linking said subset of step (a) with said separation element;

c) separating said linked molecules; and

d) detecting one or more nucleic acid sequence differences with respect to a reference sequence in the members of said separated molecules of step (c) with a method capable of detecting one or more nucleotide differences with respect to a reference sequence.

18. The method of claim 17 wherein said method capable of detecting one or more nucleotide differences comprises DNA sequencing.

19. The method of claim 17 wherein said method capable of detecting one or more nucleotide differences comprises denaturing HPLC.

20. The method of claim 17 wherein said method capable of detecting one or more nucleotide differences comprises electrophoresis capable of detecting conformational differences in the nucleic acids.

21. The method of claim 17 wherein said method capable of detecting one or more nucleotide differences comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid.

22. The method of claim 18 wherein said sequencing is performed using primers that hybridize to the sequences capable of being operatively linked to a separation element.

23. The method of claim 17 wherein said cleavage agents are restriction endonucleases.

24. The method of claim 23 wherein at least one restriction endonuclease cleaves DNA infrequently.

25. The method of claim 24 wherein the infrequently cleaving restriction endonuclease is selected from the group consisting of AscI, BssHII, EagI, NheI, NotI, PacI, PmeI, RsrII, SalI, SbfI, SfiI, SgrAI, SpeI, SrfI, and SwaI restriction endonucleases.

26. A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) fragmenting a nucleic acid sample from one or more individuals to an average fragment length;

b) physically separating a subset of the nucleic acid fragments generated in step (a) based on the presence or absence of a particular nucleotide sequence within said fragments;

c) operatively linking said subset of step (b) with molecules capable of being replicated;

d) introducing the linked molecules of step (c) into a system capable of replicating said linked molecules, and replicating said linked molecules to form a collection of replicated molecules; and

e) detecting a nucleic acid sequence difference with respect to a reference sequence in the collection of replicated molecules of step (d) using a method capable of detecting one or more nucleotide differences with respect to a reference sequence.

27. The method of claim 26 wherein said system capable of replicating said linked molecules comprises host cells and said collection of replicated molecules comprises a library.

28. The method of claim 26 wherein said method capable of detecting one or more nucleotide differences comprises DNA sequencing.

29. The method of claim 26 wherein said method capable of detecting one or more nucleotide differences comprises denaturing HPLC.

30. The method of claim 26 wherein said method capable of detecting one or more nucleotide differences comprises electrophoresis capable of detecting conformational differences in the nucleic acids.

31. The method of claim 26 wherein said method capable of detecting one or more nucleotide differences comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid.

32. The method of claim 28 wherein said DNA sequencing is performed using primers that hybridize to the molecules capable of being replicated.

33. The method of claim 26 wherein said system capable of replicating said linked molecules comprises in vitro replication of said linked molecules.

34. The method of claim 33 wherein said in vitro replication comprises a step utilizing primers for nucleic acid polymerization that hybridize specifically to said molecules capable of being replicated.

35. The method of claim 33 wherein said in vitro replication is repeated one or more times to increase the enrichment of said linked molecules.

36. The method of claim 33 wherein said in vitro replication comprises a step utilizing primers for nucleic acid polymerization that hybridize specifically to sequences comprising both a segment of said molecules capable of being replicated and the fragment ends of a subset of the nucleic acid molecules linked to said molecules capable of being replicated.

37. The method of claim 26 wherein the method used to physically separate a subset of fragments comprises using a sequence-specific binding molecule.

38. The method of claim 37 wherein the sequence-specific binding molecules is a protein.

39. The method of claim 26 wherein said fragmenting is performed using one or more sequence-specific cleavage agents.

40. The method of claim 39 wherein said sequence-specific cleavage agents are restriction endonucleases.

41. A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) fragmenting a nucleic acid sample from one or more individuals to an average fragment length;

b) separating a subset of the nucleic acid fragments based on the presence or absence of a nucleotide sequence within said fragments;

c) detecting one or more nucleic acid sequence differences with respect to a reference sequence in the members of said separated molecules of step (b) with a method capable of detecting one or more nucleotide differences with respect to a reference sequence.

42. The method of claim 41 wherein said method capable of detecting one or more nucleotide differences comprises DNA sequencing.

43. The method of claim 41 wherein said method capable of detecting one or more nucleotide differences comprises denaturing HPLC.

44. The method of claim 41 wherein said method capable of detecting one or more nucleotide differences comprises electrophoresis capable of detecting conformational differences in the nucleic acids.

45. The method of claim 41 wherein said method capable of detecting one or more nucleotide differences comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid.

46. The method of claim 42 wherein said DNA sequencing is performed using primers that hybridize to the molecules capable of being replicated.

47. The method of claim 41 wherein the method used to physically separate a subset of fragments comprises using a sequence-specific binding molecule.

48. The method of claim 47 wherein the sequence-specific binding molecule is a protein.

49. A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) hybridizing a nucleic acid sample from one or more individuals with oligonucleotide primers under conditions wherein each of said primers permits extension by a polymerase at two or more different sequences, and wherein the sequences replicated by

extension of said primers comprise regions where there are known sequence differences between individuals of the species being examined;

b) extending said oligonucleotide primers hybridized in step (a) to form an enriched collection of replicated molecules; and

c) detecting one or more nucleic acid sequence differences in the members of said collection with respect to a reference sequence with a method capable of detecting one or more nucleotide differences with respect to a reference sequence.

50. The method of claim 49 wherein said method capable of detecting one or more nucleotide differences comprises DNA sequencing.

51. The method of claim 49 wherein said method capable of detecting one or more nucleotide differences comprises denaturing HPLC.

52. The method of claim 49 wherein said method capable of detecting one or more nucleotide differences comprises electrophoresis capable of detecting conformational differences in the nucleic acids.

53. The method of claim 49 wherein said method capable of detecting one or more nucleotide differences comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid.

54. The method of claim 50 wherein said DNA sequencing is performed using primers that hybridize to the primers hybridized in step (a) and extended in step (b).

55. The method of claim 49 wherein steps (a)-(b) are repeated one or more times to increase the enrichment of said enriched collection of replicated molecules.

56. The method of claim 49 wherein said method further comprises, after step (b) and before step (c) the step of hybridizing a second set of primers that hybridize specifically to sequences comprising both a segment of said first set of primers and a segment of the replicated portion of the molecules generated in step (b).

57. A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) fragmenting a nucleic acid sample from one or more individuals;

b) physically separating a subset of said nucleic acid fragments based on the size of the fragments.

c) operatively linking said subset of step (b) with molecules capable of being replicated;

d) introducing the linked subset of molecules of step (c) into a system capable of replicating said linked subset of molecules, and replicating said subset of linked molecules to form an enriched collection of replicated molecules; and

e) detecting one or more nucleotide sequence differences in the members of said collection of step (d) with a method capable of detecting one or more nucleotide differences with respect to a reference sequence.

58. The method of claim 57 wherein said system capable of replicating said linked molecules comprises host cells and the collection of replicated molecules comprises a library.

59. The method of claim 57 herein said method capable of detecting one or more nucleotide differences comprises DNA sequencing.

60. The method of claim 57 wherein said method capable of detecting one or more nucleotide differences comprises denaturing HPLC.

61. The method of claim 57 wherein said method capable of detecting one or more nucleotide differences comprises electrophoresis capable of detecting conformational differences in the nucleic acids.

62. The method of claim 57 herein said method capable of detecting one or more nucleotide differences comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid.

63. The method of claim 59 wherein said sequencing is performed using primers that hybridize to the molecules capable of being replicated.

64. The method of claim 57 wherein said system capable of replicating said linked molecules comprises in vitro replication of said linked molecules.

65. The method of claim 64 wherein said in vitro replication comprises a step utilizing primers for nucleic acid polymerization that hybridize specifically to said molecules capable of being replicated.

66. The method of claim 64 wherein said in vitro replication is repeated one or more times to increase the enrichment of said collection of replicated molecules.

67. The method of claim 64 wherein said in vitro replication comprises a step utilizing primers for nucleic acid polymerization that hybridize specifically to sequences comprising both a segment of said molecules capable of being replicated and the fragment ends of a subset of the nucleic acid molecules linked to said molecules capable of being replicated.

68. The method of claim 57 wherein the physical separation by size of step (b) is accomplished using electrophoresis or density gradient centrifugation.

69. A method of enriching for and identifying nucleic acid sequence differences with respect to a reference sequence comprising:

a) fragmenting a nucleic acid sample from one or more individuals;

b) physically separating a subset of said nucleic acid fragments based on the size of the fragments;

c) detecting one or more nucleic acid sequence differences with respect to a reference sequence in the members of said separated molecules of step (b) with a method capable of detecting one or more nucleotide differences with respect to a reference sequence.

70. The method of claim 69 wherein said method capable of detecting one or more nucleotide differences comprises DNA sequencing.

71. The method of claim 69 wherein said method capable of detecting one or more nucleotide differences comprises denaturing HPLC.

72. The method of claim 69 wherein said method capable of detecting one or more nucleotide differences comprises electrophoresis capable of detecting conformational differences in the nucleic acids.

73. The method of claim 69 wherein said method capable of detecting one or more nucleotide differences comprises a protein capable of detecting mismatches between duplexed strands of nucleic acid.

74. The method of claim 69 wherein the physical separation by size of step (b) is accomplished using electrophoresis or density gradient centrifugation.

75. A method for accessing a sub-portion of a nucleic acid population, such method comprising:

a) mixing one or more oligonucleotide primers with a sample of said nucleic acid population under conditions which permit hybridization of one or more primers to said sample, each primer comprising a 3' terminal sequence which hybridizes to an anchor sequence present in said nucleic acid sample; and

b) adding deoxynucleotides and a template-dependent DNA polymerizing activity under conditions which permit extension of said one or more oligonucleotide primers, such that the population of extended primers comprises a sub-portion of nucleic acid molecules in said sample.

76. The method of claim 75 wherein said primer comprises an additional 3'-terminal extension immediately adjacent to said sequence which hybridizes to an anchor sequence.

77. The method of claim 76 wherein said additional 3' terminal extension is a mononucleotide selected from the group consisting of G, A, T and C.

78. The method of claim 76 wherein said additional 3' terminal extension is a dinucleotide selected from the group consisting of: AA; AG; AC; AT; CA; CG; CC; CT; GA; GG; GC; GT; TA; TG; TC; and TT.

79. The method of claim 76 wherein said additional 3' terminal extension is a trinucleotide selected from the group consisting of: AAA; AAC; AAG; AAT; AGA; AGC; AGG; AGT; ACA; ACC; ACG; ACT; ATA; ATC; ATG; ATT; CAA; CAC; CAG; CAT; CCA; CCC; CCG; CCT; CGA; CGC; CGG; CGT; CTA; CTC; CTG; CTT; GAA; GAC; GAG; GAT; GCA; GCC; GCG; GCT; GGA; GGC; GGG; GGT; GTA; GTC; GTG; GTT; TAA; TAC; TAG; TAT; TCA; TCC; TCG; TCT; TGA; TGC; TGG; TGT; TTA; TTC; TTG; and TTT.

80. The method of claim 76 wherein said additional 3' terminal extension is selected from the group consisting of: tetranucleotides, pentanucleotides, hexanucleotides, septanucleotides, and octanucleotides.

81. The method of any one of claims 75-80 wherein the anchor sequence is the recognition sequence for a sequence-specific DNA binding activity selected from the group consisting of: transcription factors or DNA binding domains thereof; proteins with zinc finger DNA binding domains; restriction endonuclease DNA sequence recognition domains; sequence-specific antibodies; nucleic acid molecules; oligonucleotides complementary to an adapter ligated to a population of DNA molecules; aptamers; peptide nucleic acid molecules;

peptides; and affinity resins which recognize DNA having a particular G+C content or methylation status.

82. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to between about 500 and 5000 nucleotides in length.

83. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 500 nucleotides in length.

84. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 750 nucleotides in length.

85. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 1000 nucleotides in length.

86. The method of any one of claims 75-81wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 1500 nucleotides in length.

87. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 2000 nucleotides in length.

88. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 3000 nucleotides in length.

89. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 4000 nucleotides in length.

90. The method of any one of claims 75-81 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 5000 nucleotides in length.

91. The method of any one of claims 75-90 wherein said anchor sequence is a restriction endonuclease recognition sequence.

92. The method of claim 91 wherein said restriction endonuclease recognition sequence occurs infrequently in the genome of the organism from which the nucleic acid sample is obtained.

93. The method of claim 92 wherein said restriction endonuclease recognition sequence is selected from the group consisting of : AscI, BssHII, EagI, NheI, NotI, PacI, PmeI, RsrII, SalI, SbfI, SfiI, SgrAI, SpeI, SrfI, and SwaI restriction endonuclease recognition sequences.

94. The method of any one of claims 75-93 wherein one or more of the oligonucleotides or deoxynucleotides is detectably labeled.

95. The method of claim 94 wherein the label is selected from the group consisting of: fluorescent moieties; radioactive moieties; biotin; and digoxigenin.

96. The method of any one of claims 75-95 wherein the oligonucleotide primer or primers is attached to a solid support or is labeled with a moiety allowing attachment to a solid support.

97. A method of identifying a nucleic acid sequence polymorphism comprising any one of the methods of claims 75-96 with the additional step of identifying a nucleic acid sequence polymorphism in a population of individuals.

98. A method of genotyping an individual with respect to a nucleic acid sequence polymorphism comprising any one of the methods of claims 75-96 with the additional step of identifying a nucleic acid sequence polymorphism in an individual.

99. A method for accessing a sub-population of a genome, such method comprising:

a) cleaving a nucleic acid sample with a first restriction endonuclease wherein the recognition sequence of said first restriction endonuclease occurs infrequently in the genome;

b) ligating an adapter molecule to the cleaved ends generated in step (a), said adapter having an overhang complementary to that generated by said first restriction endonuclease, and ligation of said adapter further regenerating all or part of the recognition sequence of said first restriction endonuclease;

c) mixing an oligonucleotide primer complementary to said adapter molecule, wherein the 3' terminus of said oligonucleotide primer is complementary to the regenerated recognition sequence of said first restriction endonuclease, under conditions which permit hybridization of said oligonucleotide primer to said adapter; and

d) adding deoxynucleotides and a template-dependent DNA polymerizing activity under conditions which permit extension of said oligonucleotide primer, the resulting population of primer extension products comprising a sub-portion of the molecules in said nucleic acid sample.

100. A method for accessing a sub-population of a genome, such method comprising:

a) cleaving a nucleic acid sample with one or more cleavage agents to produce nucleic acid fragments;

b) mixing one or more primers capable of annealing to nucleic acid fragment ends generated by said one or more cleavage agents and capable of initiating the replication of the nucleic acid regions comprising said fragment ends under conditions that permit said annealing;

c) incubating with a polymerizing activity under conditions that permit extension of said one or more primers, the resulting population of primer extension products comprising a sub-portion of the nucleic acid sequences in said genome, wherein said sub-portion of the nucleic acid sequences comprises an incomplete extension product.

101. The method of claim 100 wherein said cleavage agents are sequence-specific cleavage agents.

102. The method of claim 100 wherein said cleavage agents are sequence-specific cleavage agents and said primers comprise sequences complementary to the recognition sequence of said sequence-specific cleavage agents.

103. The method of claim 102 wherein said primers additionally comprise 3' end sequences capable of hybridizing to only a subset of the molecules in the nucleic acid sample.

104. The method of claim 103 wherein said 3' end sequences comprise terminal extensions immediately adjacent to the sequence that hybridizes to said recognition sequence.

105. The method of claim 104 wherein said extensions are mononucleotides selected from the group consisting of: A, C, G, and T.

106. The method of claim 104 wherein said extensions are dinucleotides selected from the group consisting of: AA; AG; AC; AT; CA; CG; CC; CT; GA; GG; GC; GT; TA; TG; TC; and TT.

107 The method of claim 104 wherein said extensions are trinucleotides selected from the group consisting of: AAA; AAC; AAG; AAT; AGA; AGC; AGG; AGT; ACA; ACC; ACG; ACT; ATA; ATC; ATG; ATT; CAA; CAC; CAG; CAT; CCA; CCC; CCG; CCT; CGA; CGC; CGG; CGT; CTA; CTC; CTG; CTT; GAA; GAC; GAG; GAT; GCA; GCC; GCG; GCT; GGA; GGC; GGG; GGT; GTA; GTC; GTG; GTT; TAA; TAC; TAG; TAT; TCA; TCC; TCG; TCT; TGA; TGC; TGG; TGT; TTA; TTC; TTG; and TTT.

108. The method of claim 104 wherein said extension is selected from the group consisting of: tetranucleotides, pentanucleotides, hexanucleotides, septanucleotides, and octanucleotides.

109. A method for accessing a sub-population of a genome, such method comprising:

a) cleaving a nucleic acid sample with one or more cleavage agents to produce nucleic acid fragments;

b) operatively linking an adapter molecule to the cleaved ends generated in step (a);

c) incubating with a polymerizing activity under conditions that permit nucleic acid synthesis from said adapter, the resulting population of extension products comprising a sub-portion of the nucleic acid sequences in said genome, wherein said sub-portion of the nucleic acid sequences comprises an incomplete extension product.

110. The method of claim 109 wherein said adapter molecule contains a transcriptional promoter.

111. The method of claim 109 wherein said adapter molecule contains a free end capable of being extended by a polymerizing activity.

112. The method of claim 109 wherein the adapter molecule is double stranded and contains a sequence capable of being nicked by a second cleavage agent to produce a free end capable of being extended by a polymerizing activity.

113. A method for accessing a sub-population of a genome, such method comprising:

a) cleaving a nucleic acid sample with one or more cleavage agents to produce nucleic acid fragments;

b) operatively linking an adapter molecule to the cleaved ends generated in step (a);

c) mixing a primer complementary to said adapter molecule with the linked molecules generated in step (b) under conditions that permit hybridization of said primer to said adapter; and

d) incubating with a polymerizing activity under conditions that permit nucleic acid synthesis from said adapter, the resulting population of primer extension products comprising a sub-portion of said genome, wherein said sub-portion of said genome comprises an incomplete extension product.

114. The method of claim 113 wherein said cleavage agents are sequence-specific cleavage agents.

115. The method of claim 113 wherein said cleavage agents are sequence-specific cleavage agents and said primers comprise sequences complementary to the recognition sequence of said sequence-specific cleavage agents.

116. The method of claim 115 wherein said primers additionally comprise 3' end sequences capable of hybridizing to only a subset of the molecules in the nucleic acid sample.

117. The method of claim 116 wherein said 3' end sequences comprise terminal extensions immediately adjacent to the sequence that hybridizes to the recognition sequence.

118. The method of claim 117 wherein said extensions are mononucleotides selected from the group consisting of: A, C, G, and T.

119. The method of claim 117 wherein said extensions are dinucleotides selected from the group consisting of: AA; AG; AC; AT; CA; CG; CC; CT; GA; GG; GC; GT; TA; TG; TC; and TT.

120. The method of claim 117 wherein said extensions are trinucleotides selected from the group consisting of: AAA; AAC; AAG; AAT; AGA; AGC; AGG; AGT; ACA; ACC; ACG; ACT; ATA; ATC; ATG; ATT; CAA; CAC; CAG; CAT; CCA; CCC; CCG; CCT; CGA; CGC; CGG; CGT; CTA; CTC; CTG; CTT; GAA; GAC; GAG; GAT; GCA; GCC; GCG; GCT; GGA; GGC; GGG; GGT; GTA; GTC; GTG; GTT; TAA; TAC; TAG; TAT; TCA; TCC; TCG; TCT; TGA; TGC; TGG; TGT; TTA; TTC; TTG; and TTT.

121. The method of claim 117 wherein said extensions are selected from the group consisting of: tetranucleotides, pentanucleotides, hexanucleotides, septanucleotides, and octanucleotides.

122. A method for accessing a sub-population of a genome, such method comprising:

a) cleaving a nucleic acid sample with a cleavage agent;

b) operatively linking an adapter molecule to the cleaved ends generated in step (a), said adapter having an end compatible with that generated by said cleavage agent;

c) mixing a primer complementary to said adapter molecule, wherein the 3' terminus of said primer is complementary to the recognition sequence of said cleavage agent, under conditions that permit hybridization of said primer to said adapter; and

d) adding deoxynucleotides and a template-dependent polymerizing activity under conditions that permit extension of said oligonucleotide primer, the resulting population of primer extension products comprising a sub-portion of said genome.

123. The method of claim 122 wherein said cleavage agents are sequence-specific cleavage agents.

124. The method of claim 122 wherein said cleavage agents are sequence-specific cleavage agents and said primers comprise sequences complementary to the recognition sequence of said sequence-specific cleavage agents.

125. The method of claim 124 wherein said primers additionally comprise 3' end sequences capable of hybridizing to only a subset of the molecules in the nucleic acid sample.

126. The method of claim 125 wherein said 3' end sequences comprise terminal extensions immediately adjacent to the sequence that hybridizes to the recognition sequence

127. The method of claim 126 wherein said extensions are mononucleotides selected from the group consisting of: A, C, G, and T.

128. The method of claim 126 wherein said extensions are dinucleotides selected from the group consisting of: AA; AG; AC; AT; CA; CG; CC; CT; GA; GG; GC; GT; TA; TG; TC; and TT.

129. The method of claim 126 wherein said extensions are trinucleotides selected from the group consisting of: AAA; AAC; AAG; AAT; AGA; AGC; AGG; AGT; ACA; ACC; ACG; ACT; ATA; ATC; ATG; ATT; CAA; CAC; CAG; CAT; CCA; CCC; CCG; CCT; CGA; CGC; CGG; CGT; CTA; CTC; CTG; CTT; GAA; GAC; GAG; GAT; GCA; GCC; GCG; GCT; GGA; GGC; GGG; GGT; GTA; GTC; GTG; GTT; TAA; TAC; TAG; TAT; TCA; TCC; TCG; TCT; TGA; TGC; TGG; TGT; TTA; TTC; TTG; and TTT.

130. The method of claim 126 where in said extensions are selected from the group consisting of: tetranucleotides, pentanucleotides, hexanucleotides, septanucleotides and octanucleotides.

131. The method of any one of claims 99-130 wherein an amount of chain-terminating deoxynucleotide analogs is added sufficient to limit the length of the average extension product to between about 500 and 5000 nucleotides.

132. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 500 nucleotides in length.

133. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 750 nucleotides in length.

134. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 1000 nucleotides in length.

135. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 1500 nucleotides in length.

136. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 2000 nucleotides in length.

137. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 3000 nucleotides in length.

138. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 4000 nucleotides in length.

139. The method of any one of claims 99-130 wherein an amount of chain-terminating nucleotide analogs is added sufficient to limit the average extension product to approximately 5000 nucleotides in length.

140. The method of any one of claims 99-130 wherein said oligonucleotide primer or one or more of said deoxynucleotides is detectably labeled.

141. The method of claim 140 wherein the label is selected from the group consisting of: fluorescent moieties; radioactive moieties; biotin; and digoxigenin.

142. The method of any one of claims 99-141 wherein said oligonucleotide primer is attached to a solid support.

143. A method of identifying a nucleic acid sequence polymorphism comprising any one of the methods of claims 99-142 with the additional step of identifying a nucleic acid sequence polymorphism in a population of individuals.

144. A method of genotyping an individual with respect to a polymorphism comprising any one of the methods of claims 99-142 with the additional step of identifying a nucleic acid sequence polymorphism in an individual.

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